What is the Role of Environmental Chemicals in the Development of Type 1 Diabetes?
Public Comment for the NTP Workshop on the Role of Environmental Chemicals in the Development of Diabetes and Obesity, Jan. 11-13, 2011.

While the focus of this workshop is on the role of environmental chemicals in the development of type 2 diabetes, there are a number of reasons why the research discussed at this workshop might be relevant for type 1 diabetes as well. Indeed, the role of environmental chemicals in the development of type 1 diabetes is a current research gap waiting to be filled.

The increasing incidence of type 1 diabetes in children is still unexplained

Despite the recent explosion of studies on type 2 and environmental chemicals, there are only a handful of studies on type 1 and these chemicals (Kolachi et al. 2010; Rignell-Hydbom et al. 2010; Hathout et al. 2006; Longnecker et al. 2001). (The role of nitrate/nitrite/N-nitroso compounds in type 1 diabetes has been studied more extensively, and discussed in Virtanen and Knip 2003). And yet, there has been an unexplained but well-documented rise in type 1 incidence in children in industrialized countries around the world. This rise began during the time of World War 2 (Gale 2002), simultaneous with the widespread use of chemicals in industrialized countries, and has averaged about 3% per year since 1960 (Onkamo et al. 1999). Alarmingly, type 1 incidence is increasing most rapidly in children under 5, averaging 4% per year during the 1990s (Diamond Project Group 2006). Environmental chemicals have not yet been sufficiently evaluated as possible contributors to this rise.

The diabetes spectrum: overlapping types of diabetes

Why might the research discussed at this workshop be relevant for type 1 diabetes? One reason is the commonalities between type 1 and type 2 diabetes. While they are considered separate diseases, there is growing evidence of an overlap between them. In fact, we can think of diabetes as a "continuous spectrum," with autoimmune type 1 in young children at one end, and metabolic type 2 in adults at the other (Brooks-Worrell and Palmer 2010). A large portion of people with diabetes fall in the middle of the spectrum, and may have both type 1 (autoimmune) and type 2 (metabolic) processes contributing to their diabetes. Among adults, 15-35% of people diagnosed with type 2 before age 45 test positive for GAD autoantibodies (a marker of type 1 diabetes), as do 7-9% of those diagnosed at an older age (Tuomi 2005). These antibody positive adults are sometimes considered to have LADA, or Latent Autoimmune Diabetes in Adults, a slowly progressive form of autoimmune diabetes. LADA may be the same as type 1 in adults, or may be more of an intermediary between type 1 and type 2. In the UK, about 10% of adults with presumed type 2 diabetes were found to have islet cell or GAD autoantibodies and considered to have LADA (Fourlanos et al. 2005).

There are good reasons why type 1 is not called "juvenile diabetes" anymore; a recent Swedish study found that almost 60% of newly diagnosed people with type 1 were over age 40, with incidence peaking in both the under 10 and over 50 age groups (Thunander et al. 2008). Many children with diabetes show signs of both types of diabetes ("double diabetes"): autoimmune markers as well as increased insulin resistance or obesity (Pozzilli et al. 2007).

Gestational diabetes, or diabetes diagnosed during pregnancy, can be a precursor of either type 1 or type 2 later in life. About 15-30% of women with gestational diabetes have previously unrecognized type 2. And, about 10% of women with gestational diabetes have "autoimmune gestational diabetes" that is associated with the presence of islet autoantibodies and a high risk of developing type 1 (Wucher et al. 2010).

Yet even testing for autoantibodies may not be sufficient to distinguish the different types of diabetes. Brooks-Worrell et al. (2010) have identified a subgroup of type 2 patients who test negative for islet cell autoantibodies but positive for islet autoreactive T cells. They conclude that islet autoimmunity may play a role in type 2 pathogenesis as well as type 1, and may be more common than previously thought.

Most studies on contaminants and diabetes group all of these types of diabetes together. The CDC's NHANES dataset, for example, does not distinguish between different types of diabetes. This dataset has been used in a number of groundbreaking studies on contaminants and diabetes (e.g., Lang et al. 2008; Lee et al. 2006). We do not know how many people with type 1 have unrecognized type 1 or signs of immune system dysfunction. We cannot assume that all adults with diabetes or those diagnosed as adults have type 2, or even that children with diabetes have type 1. Nor can we assume that people taking insulin have type 1, since many type 2 patients rely on insulin treatment. We cannot even assume that adults with diabetes who do not take insulin have type 2, since one of the criteria for LADA is that patients do not require insulin at diagnosis, and half of LADA patients never require insulin (Tuomi 2005). Nor can we assume that people with type 2 only have metabolic processes contributing to their disease, and people with type 1 only have autoimmunity at work. But perhaps these assumptions are not important; perhaps the different types of diabetes overlap enough to be grouped together. If so, and if many people with diabetes have both metabolic and autoimmune processes contributing to their disease, then studies on contaminants and type 2 likely have relevance for type 1, and vice versa. On the other hand, a downside of grouping the different types of diabetes together is that despite the overlap, most people with diabetes have type 2, and there is an assumption that the results of studies on contaminants and diabetes are therefore only relevant for type 2 diabetes, while type 1 is entirely different. To examine the processes involved at either end of the diabetes spectrum, we should better distinguish between diabetes types.

Weight gain and insulin resistance may play a role in type 1 as well as type 2 pathogenesis

Are studies of weight gain and insulin resistance relevant for type 1 diabetes? Surprisingly, yes. While obesity is clearly associated with the development of type 2 diabetes, there is growing evidence that increased weight gain (not necessarily to the point of obesity) may contribute to type 1 diabetes development as well. For example, a recent meta-analysis found evidence for an association between higher body mass index (BMI) and increased risk for subsequent type 1 diabetes in childhood (Verbeeten et. al. 2010). There is also evidence for an association between increased insulin resistance and progression to type 1 diabetes (Xu et al. 2007). And, metabolic syndrome is common in people with type 1 diabetes, not only type 2 (Thorn et al. 2005). In fact, Wilkin (2008) hypothesizes that type 1 and 2 diabetes are one and the same disorder of insulin resistance, accompanied by different genetic backgrounds, with increased weight gain the central reason behind the increasing incidence of both types of diabetes. While most researchers do not go that far, his ideas have triggered a number of studies (many supporting his hypothesis), and spurred a lively debate in the scientific literature. This workshop will evaluate studies that have found associations between contaminant exposures and increased insulin resistance and weight gain, factors that may indeed have significance for type 1 diabetes development.

The immune system may play a role in type 2 as well as type 1 pathogenesis

Due to the increasing evidence of immune system abnormalities in people with type 2 diabetes, we should keep in mind the possible role of immunotoxicants in the development of all types of diabetes. While this workshop is not addressing immunotoxicants *per se*, exposure to a number of the contaminants discussed here, such as bisphenol A (BPA), some heavy metals, and some persistent organic pollutants (POPs) have been associated with increased signs of autoimmunity and other immune system effects in animals or humans (e.g., Yurino et al. 2004; Hemdan et al. 2007). For example, one study has found increased levels of GAD autoantibodies in employees at a factory that produced PCBs (Langer et al. 2002). It may be important to include measurements of immune system parameters and autoimmunity in studies of contaminants and diabetes.

Dietert et al. (2010) propose looking at patterns of disease that begin in childhood and involve inflammatory processes, such as metabolic syndrome (inflammatory dysfunction) and autoimmune conditions. These authors point out that adipose tissue functions much like an immune organ, and that obesity can be considered a low-grade inflammatory state. Metabolic syndrome and immune dysfunction can be established early in life, even though disease onset may not occur until adulthood. Similarly, signs

of immune dysfunction and autoimmunity may appear very early in life in type 1 diabetes (even *in utero*), with disease onset much later. People with type 1 are also at higher risk of other autoimmune diseases (Narendran et al. 2005). Could endocrine disruptors play a role in both autoimmune and metabolic diabetes development via disruption of immune system development and metabolic processes? Atkinson and Gale (2003) suggest a model to study type 1 diabetes that incorporates growth and development in addition to genes and environment. This model entails examining the interactions among the developing immune system, genetic response, and the timing, duration, and combination of environmental exposures. Contaminant exposures can begin *in utero* (or perhaps even earlier, via epigenetic or other effects), and could help to explain this immune system dysfunction later in life. Interestingly, the original studies on N-nitroso compounds and type 1 diabetes found that the diabetogenic effects of these compounds occurred in the offspring as a result of dietary consumption by the parents around the time of conception (Helgason et al. 1982; Helgason and Jonasson 1981). Timing of exposure, then, may be critical.

Beta cell destruction plays a role in type 1 and type 2 diabetes

This workshop will examine evidence that chemicals such as BPA and pesticides can affect beta cell function and insulin secretion. Dahlquist (2006) proposes that environmental factors that overload or stress beta cells may make these cells more susceptible to an autoimmune attack, and hasten the appearance of type 1 diabetes. These factors, in turn, could be largely responsible for the increasing incidence of type 1 in children. She lists a number of factors that could overload beta cells, including increased insulin resistance due to excess weight gain, increased insulin requirements due to high growth rates, physical stress (infection, inflammation), or psychological stress. Should environmental chemicals be added to this list? Studies that show the effects of contaminants on beta cells are relevant for type 1 diabetes, as well as type 2, since beta cell destruction is common to both (although the mechanisms leading to this destruction may differ) (Cnop et al. 2005).

Additional areas for future research

One of the goals of this workshop is to identify data gaps and areas for future research. One such gap is the role of vitamin D deficiency in both type 1 (Hypponen 2010) and type 2 (Palomer et al. 2008) diabetes development. There is preliminary evidence that exposure to contaminants can affect vitamin D synthesis in animals (Lilienthal et al. 2000). Could contaminants contribute to diabetes pathogenesis by interfering with vitamin D synthesis? Another data gap is the role of the intestine in both type 1 and type 2 diabetes. Increased intestinal permeability and inflammation have been found in patients with type 1 diabetes (Vaarala 2008). Interestingly, type 2 has gone into remission after gastric bypass surgery, in which food bypasses part of the small intestine (Pournaras et al. 2010). Why? Could contaminant exposures be related to the intestine in diabetes? Some exposures have been found to affect intestinal inflammation or permeability in animals or intestinal cells (e.g., Braniste et al. 2010; Choi et al. 2010). And, many chemical exposures occur via food.

Breastmilk can support immune system development (Jackson and Nazar 2006). It is therefore curious that many recent prospective studies have not found breastfeeding to be protective against type 1 related autoimmunity. More surprisingly, one study found that islet autoimmunity risk was lowest in children who had never breastfed, and highest in children who breastfed the longest (Ziegler et al. 2003). Could the higher levels of contaminants in breastmilk than in formula help to explain this finding? Additional data gaps include examining the role of contaminants in exacerbating the diabetogenic effects of viruses and stress.

Which contaminants should be studied in relation to type 1 diabetes?

Elucidating the role of contaminants in the pathogenesis of type 1 diabetes is an important area for future research. There are a number of on-going, prospective studies of type 1 diabetes currently underway; most of them do not include measurements of exposures to any of the chemicals discussed in this workshop. Yet many of these contaminants show effects that may be relevant for type 1 diabetes

development. One outcome of this workshop should be to identify contaminants to include in studies that focus on type 1 diabetes in children. These studies may help to identify the reasons behind the increasing incidence of type 1 diabetes in children, and perhaps help to prevent this disease.

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www.diabetesandenvironment.org
a website summarizing current scientific research on diabetes and the environment, focusing on type 1
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Pub Med ID numbers follow each citation (PM:).

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